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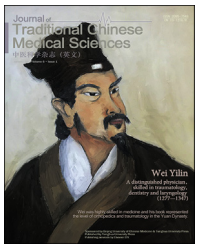

Combination therapy of scalp electro-acupuncture and medication for the treatment of Parkinson's disease: A systematic review and meta-analysis

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KEYWORDS
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Motor function

Abstract *Objective:* To summarize the current clinical evidence related to the therapeutic effects and safety of adjuvant scalp electro-acupuncture (SEA) treatment for Parkinson's disease in China.
Methods: Following the PRISMA statement, seven electronic databases were searched to retrieve randomized controlled clinical trials that used SEA combined with medication as the treatment intervention, and medication as the control. RevMan 5.3 was used to analyze outcomes, including the Unified Parkinson's Disease Rating Scale (UPDRS), Webster scale, effectiveness rate, and UPDRS III.
Results: Nine randomized controlled trials, with certain methodological flaws and risks of bias, were included that involved 474 participants. SEA combined with medication was more effective than medication alone in overall therapeutic effects, as evidenced by total UPDRS scores (mean difference (MD): 7.15, 95% confidence interval [CI] 0.24 to 14.07, $P = .04$), Webster scores (MD: 1.60, 95% CI 0.20 to 2.99, $P = .03$), and effectiveness rate (risk ratio: 1.35, 95% CI 1.19 to 1.54, $P < .001$). In addition, there was significant improvement in pooled motor

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function results after adjuvant SEA treatment compared with medication alone (MD: 5.75, 95% CI 4.18 to 7.32, $P < .001$).
Conclusion: The combination of SEA and medication may be a promising intervention for patients with Parkinson's disease, especially to improve motor function. However, results were inconclusive, and additional studies with rigorous experimental design and larger sample sizes are needed to verify these results.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by selective mesencephalic dopamine neuron deficiency, and it presents with motor, non-motor, and behavioral dysfunctions.[1] The diagnosis of PD is primarily based on clinical motor symptoms, including tremor, rigidity, akinesia or bradykinesia, and postural instability, of which tremor or rigidity is essential for diagnosis.[2] At present, drugs and surgical therapy are the cardinal treatments and aim to alleviate symptoms, but these treatments cannot cure the disease.[3] Drug therapy can be divided into six categories, including dopamine-like drugs, dopamine agonists, monoamine oxidase B inhibitors, amantadine, anticholinergic drugs, and levodopa catechol-O-methyltransferase inhibitors.[4] Deep brain stimulation, which is outstanding in the treatment of motor symptoms, is a more recent alternative to ablative procedures; however, it has the risk of stimulating neighboring structures and brain regions, thus inducing adverse psychiatric effects.[5]

Acupuncture, an alternative medicine, is an ancient traditional Chinese medical practice that exerts a wide range of effects.[6] In traditional Chinese medicine (TCM), disease is caused by an unbalanced flow of qi, which flows in the body through the meridian system.[7,8] Stimulating acupoints to help the qi flow circulate is believed to restore the body's homeostasis.[9] Scalp acupuncture (SA) therapy has been developed through medical practice, and is a combined concept of the meridian theory from TCM and the functional localization theory of the cerebral cortex from modern medicine.[10] There are two main theoretical bases for SA: one is based on the traditional theory of *zang-fu* organs, meridians; the other is based on cerebral projections on the scalp, is known as the SA standard system, and contains 14 microsystem scalp point (MS) lines. In this practice, scalp acupoints, with specific physical locations targeting the respective regions of the brain, are penetrated with slender, sterile metal needles.[11] With the aid of modern technology, scalp electro-acupuncture (SEA) has advantages over SA. It has been shown that SEA is effective in treating neurological diseases by directly exciting the cerebral cortex, with a series of advantages over traditional SA including prolonged stimulation time, controllable stimulation, fewer side effects, and simplicity.[12–14] In addition, SEA can be combined with other therapies to increase its effectiveness. A combination of SEA and medication has been reported to exert positive effects in treating PD, but lack of strong evidence. This systematic review and meta-analysis was designed to evaluate the therapeutic effect of SEA combined with western drugs on PD using a comprehensive literature search.

Materials and methods

This systematic review was performed using the PRISMA statement as its basis.

Search strategy

A computerized search in PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), WanFang Database (WanFang), Chinese Scientific Journals Database (VIP), and Chinese Biomedical Literature Database (SinoMed) was performed independently by two reviewers (WDF and HJM). The publication timeframe was from the inception of each database until August 2018. No limit was placed on publication language. The search strategies, set according to the search instructions of the various databases, are listed in Supplementary table. MeSH terms and key words such as "acupuncture" and "Parkinson's disease" were selected. No language limit was set for the electronic search. The review authors also screened the references of relevant reviews and retrieved any relevant referenced articles to achieve optimal search results.

Criteria for considering studies for this review

All randomized controlled trials (RCTs) that evaluated SEA therapy for PD were included. Participants diagnosed with PD using standard diagnostic criteria were enrolled, without regard for age, gender, educational status, race, or disease duration. Participants who were diagnosed with a parkinsonian syndrome or with severe complications were excluded. Patients had not previously received any surgical or acupuncture interventions. The intervention in the experimental group was SEA combined with medication, without regard for treatment duration or frequency, and the intervention in the control group was medication alone. The interventions in the two treatment groups did not include any other drugs, surgery, or alternative medical interventions. The use of the Unified Parkinson's Disease Rating Scale (UPDRS) and Webster Scale as assessment methods was considered reasonable.[15,16] In addition, studies that took the effectiveness rate as an evaluation index were included.

Data collection and analysis

Study selection

Two reviewers (WDF and HJM) independently screened study titles and abstracts to exclude unrelated records. Full text retrieval and further assessment was conducted for each potentially eligible study. Any disagreements were resolved through consensus. For articles that had been published multiple times using the same data, the one with the most complete data set was selected. In cases where related data were not presented, authors were contacted for additional data.

Data extraction and management

Data extraction was completed by two authors (YC and CG) using a pre-piloted extraction sheet. Data extracted included the author, publication year, sample size, patient characteristics (age, gender, diagnosis, and disease duration), acupuncture points and frequency, dose of medication, course of treatment, outcome measures, dropouts, and adverse effects. The data extracted were cross-checked and any inconsistencies were resolved by discussion or recourse to a third author (YZ).

Risk of bias assessment

The risk of bias assessment included seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The risk of bias was evaluated using the Cochrane risk of bias tool by the two aforementioned authors (YC and CG), independently.[17] For each domain, studies were classified as having "low risk of bias", "high risk of bias", or "unclear risk of bias" based on a number of signaling questions. If necessary, consultation with a third author (YZ) occurred.

Data analysis

Measures of treatment effect. To measure the treatment effect, a mean difference (MD) with 95% confidence interval (CI) was used for continuous data, and a risk ratio (RR) with 95% CIs for dichotomous outcomes.

Assessment of heterogeneity. Based on the Cochrane Handbook guidelines, heterogeneity was evaluated using the chi-squared test. The heterogeneity was recognized as significant if the I^2 value exceeded 50%.

Assessment of publication bias. If more than 10 trials were included in the review, a funnel plot could be employed to detect publication bias.

Data synthesis. RevMan 5.3 was used to synthesize the data.[18] If heterogeneity among the trials was low ($I^2 < 50\%$), a fixed-effect model was conducted; otherwise, a random-effect model was applied.

Sensitivity analysis. A sensitivity analysis was conducted to test the stability of the results according to sample size.

Subgroup analysis. A subgroup analysis by intervention duration was conducted to investigate the effectiveness rate, depending on the scale used to assess syndrome severity. Another subgroup analysis was conducted according to the different medications used to treat PD.

Results

Literature search

Using a comprehensive electronic search, 668 potentially relevant articles were retrieved: 64 from PubMed, 66 from Embase, 42 from Cochrane Library, 183 from CNKI, 121 from WanFang, 87 from VIP, and 105 from SinoMed. After the removal of duplicates, 342 records were screened by title and abstract. Thirty studies then entered the stage of full-text screening. Of these, 22 studies were removed, 10 because of a combination of inappropriate interventions, 5 because they contained duplicate data, and 7 because they had an undesired outcome. Additionally, 3 relevant systematic reviews of acupuncture therapy and PD were retrieved for supplementation, and one trial was added. Finally, nine studies[19–27] were considered eligible for the review (Fig. 1).

Characteristics of the included studies

The nine included clinical trials were all published in China between 2006 and 2018. The mean age at inclusion ranged between 55 and 70 years old, and the sample size was from 30 to 80 participants. No RCT reported sample size calculations. The RCTs used medication as the control group and SEA combined with medication as the experimental group. The most common treatment duration of the included experiments was 4 weeks, which was also the shortest treatment time, and the longest duration was up to 12 weeks. The main acupoints used in these studies included *Dingnie Qianxiexian* (MS6), *Fengchi* (GB 20), *Dingpangxian* I (MS8), *Dingpangxian* II (MS9), *Epangxian* III (MS4), and *Zhenxia Pangxian* (MS14), of which MS6 and GB 20 were the most commonly used (Table 1).

Methodological quality

All included trials reported that the grouping was random; however, only three studies[23,25,27] were assessed as having a low risk of selection bias because they used a random numbers table to assign patients. All RCTs were evaluated with unclear risk of bias because they did not mention the allocation concealment. No article provided details about any blinding of outcome assessment, and so all studies were evaluated as having a high risk of performance bias. In all included RCTs, the number of subjects enrolled was consistent with the numbers in the statistical analysis. Six trials[19,21,23,25–27] reported important outcomes (with symptom assessment as the primary outcome), which were considered as having a low risk for selective outcome reporting bias. Only one trial[24] reported the effectiveness rate without symptom assessment, and showed a high risk of bias. The two remaining RCTs[20,22] were considered to have an unclear risk for selective outcome reporting bias because they reported the motor score without any

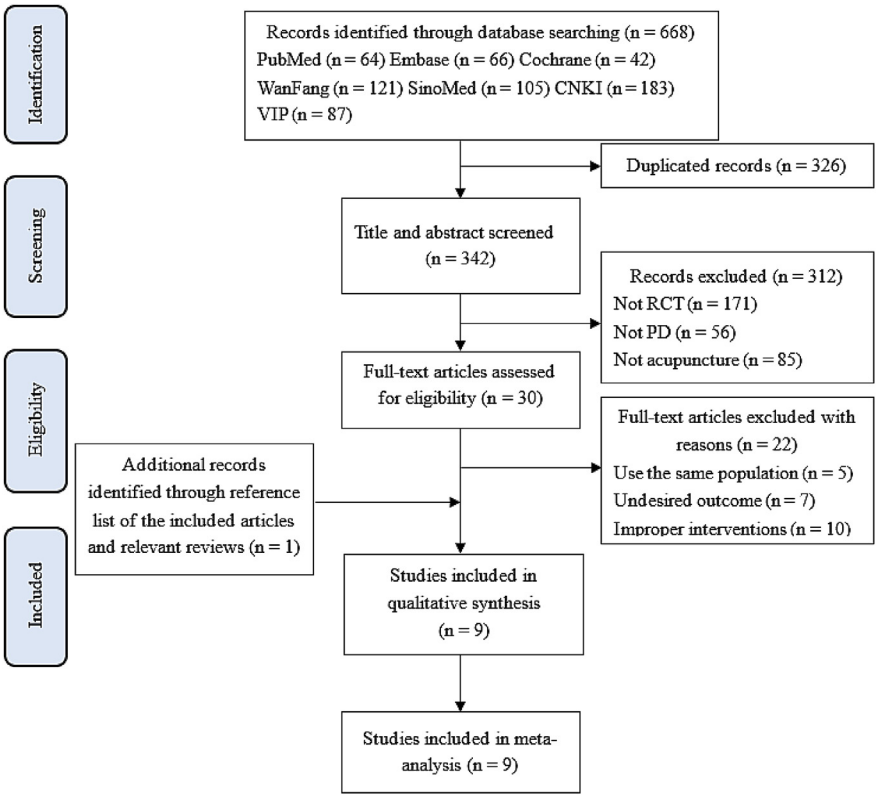

Figure 1 Study flow diagram.

description of whether they tested other subscores of UPDRS. The details of quality assessment can be seen in Figs. 2 and 3.

Results of the meta-analysis

Total UPDRS scores

Three studies[19,23,27] compared the effects of the combined treatment on total UPDRS scores (Table 2 and Supplementary Fig. 1). Since the heterogeneity was relatively high ($P = .13$; $I^2 = 52\%$), a random-effect model was conducted for the meta-analysis. The results showed that SEA combined with medication was significantly more effective than medication alone (MD: 7.15, 95% CI: 0.24 to 14.07, $P = .04$). The relatively high heterogeneity may be due to the different drugs used to treat PD, because Yang et al.[27] from the pooled analysis used L-3,4-dihydroxyphenylalanine (L-Dopa) as medication, while the other studies used Madopar. A subgroup meta-analysis was therefore performed.

In the Madopar subgroup,[19,23] the between-study heterogeneity significantly decreased ($P = .56$; $I^2 = 0\%$), and the result of the meta-analysis was not significantly different from the complete analysis (MD: 11.01, 95% CI: 4.10 to 17.91, $P = .002$), thus demonstrating that the overall effect of SEA combined with Madopar was significantly more effective than Madopar alone.

In the L-Dopa subgroup,[27] the effect of reducing total UPDRS scores in PD patients was not in significant difference between SEA combined with L-Dopa and L-Dopa alone (MD: 2.10, 95% CI: −3.56 to 7.76, $P = .47$).

Webster scale

Two studies[21,27] compared the effects of the combined treatment using the Webster scale (Table 2 and Supplementary Fig. 2). Since no obvious between-study heterogeneity existed ($P = .18$; $I^2 = 44\%$), a fixed-effect model was utilized. Results demonstrated that the combination of SEA and medication was significantly more effective than medication alone (MD: 1.60, 95% CI: 0.20 to 2.99, $P = .03$). To explore the different effects of medications on Webster scores, a subgroup analysis was conducted.

One article[21] used Madopar as the medication, and the meta-analysis showed that the effect of SEA combined with Madopar was the same as with Madopar alone in reducing Webster scores in PD patients (MD: 0.06, 95% CI: −1.43 to 2.63, $P = .56$).

The other article[27] used L-Dopa as the medication, and the meta-analysis showed that SEA combined with L-Dopa was more effective than L-Dopa alone at reducing Webster scores in patients with PD (MD: 2.50, 95% CI: 0.57 to 4.43, $P = .01$).

Effectiveness rate

Six RCTs[21,23–27] adopted the effectiveness rate as the outcome assessment (Table 2 and Supplementary Fig. 3). After treatment, patients with PD were dichotomized as effectiveness or invalidity according to the Nimodipine method.[28] If the reduction rate in symptom scores was at least 20% from before to after treatment, the treatment was considered effective; if not, it was considered to be invalid. Meta-analysis showed that the combination of SEA

Table 1 Characteristics of the included trials.

Study ID	Participates (T: Treatment; C: Control)	Intervention	Control	Treatment duration	Outcome measures
Gu K 2013[19]	Gender (male/female): T 10/13; C 15/10 Age (yrs, MD (SD)): T 66 (8); C 70 (8)	Madopar + SEA: acupoints including *Dingnie Qianxiexian* (MS6), *Fengchi* (GB 20), *Quchi* (LI 11), *Hegu* (LI 4), *Taichong* (LR 3), *Taixi* (KI 3), *Yanglingquan* (GB 34) and retained for 20 minutes.	Madopar	Once every two days, 12 weeks	Total UPDRS + UPDRS I–IV + effectiveness rate
Huang Y 2009[20]	Gender (male/female): T 8/7; C 6/9 Age (yrs, MD (SD)): T 66 (8); C 70 (8)	Madopar + SEA: acupoints including MS6, *Epangxian* III (MS4), *Dingpangxian* I (MS8), *Dingpangxian* II (MS9), *Zhenxia Pangxian* (MS14) and retained for 30 minutes	Madopar Mild: 125 mg tid Moderate: 250 mg tid	Once per day, 6 days per week, 5 weeks	UPDRS III
Jiang XM 2006[21]	T 15; C 15 Age (yrs, range): T 53—75; C 40–72	Madopar + SEA: acupoints including MS6, MS4, MS8, MS9, MS14 and retained for 30 minutes	Madopar	6 weeks	Webster + effectiveness rate
Liu XT 2016[22]	Gender (male/female): T 9/11; C 12/8 Age (yrs, MD (SD)): T 59 (8); C 63 (4)	Madopar + SEA: acupoints including bilateral chorea trembling control area and retained for 20 minutes	Madopar	10 weeks	UPDRS III
Suo QF 2015[23]	Gender (male/female): T 23/12; C 25/10 Age (yrs, MD (SD)): T 67.2 (5.6); C 66.8 (5.8)	Madopar + SEA: acupoints including GB 20, *Gongxue* (new acupoint, 1 finger *cun* inferior GB 20), chorea trembling control area and retained for 30 minutes	Madopar 125 mg tid	4 weeks	Total UPDRS + effectiveness rate
Tian J 2007[24]	Gender (male/female): T 23/17; C 22/18 Age (yrs, range): T 43—77; C 42–75	Madopar + SEA: acupoints including bilateral *Sishencong* (EX-HN1), *Xuanli* (GB 6), *Baihui* (GV 20), *Qubin* (GB 7), *Naokong* (GB 19), GB 20 and retained for 30 minutes	Madopar 125—250 mg tid	4 weeks	effectiveness rate
Wang S 2006[25]	Gender (male/female): T 25/12; C 21/18 Age (yrs, MD (SD)): T 62.1 (8.7); C 59.1 (12.4)	Madopar + SEA: acupoints including EX-HN1, GB 6, *Qianding* (GV 21), *Xuanlu* (GB 5), *Naohu* (GV 17), *Fengfu* (GV 16), *Yuzhen* (BL 9), *Tianzhu* (BL 10), GB 19, GB 20 and retained for 30 minutes	Madopar	4 weeks	Total UPDRS + effectiveness rate
Wang ZJ 2018[26]	Gender (male/female): T 20/10; C 22/8 Age (yrs, MD (SD)): 56 (5.6); 55 (6.1)	Madopar + SEA: acupoints including MS6, MS4, MS8, MS9, MS14, chorea trembling control area and retained for 30 minutes	Madopar	4 weeks	UPDRS III + effectiveness rate
Yang XY 2016[27]	Gender (male/female): T 14/6; C 11/9 Age (yrs, MD (SD)): 56 (5.6); 55 (6.1)	L-Dopa + SEA: acupoints including GV 16, GV 17, GV 20, *Yintang* (GV 29), *Shuigou* (GV 26) and retained for 30 minutes	L-Dopa	4 weeks	Total UPDRS + Webster + effectiveness rate

Abbreviations: L-Dopa; L-3,4-dihydroxypheylalanine; MD: mean difference; SD: standard deviation; SEA: scalp electro-acupuncture; UPDRS, Unified Parkinson Disease Rating Scale.

and medication had a greater effect than medication alone (RR: 1.35, 95% CI: 1.19 to 1.54, $P < .001$), and there was no heterogeneity ($P = .53$; $I^2 = 0\%$). To explore the roles of different medications, a subgroup analysis was performed.

The meta-analysis of the five RCTs[21,23–26] that used Madopar as the intervention medication demonstrated that the combination of SEA and Madopar was more effective than medication alone (RR: 1.37, 95% CI: 1.19 to 1.58, $P < .001$).

The meta-analysis of the one RCT[27] that used L-Dopa demonstrated that a combination of SEA and L-Dopa was no different than treatment with L-Dopa alone (RR: 1.21, 95% CI: 0.86 to 1.71, $P = .26$).

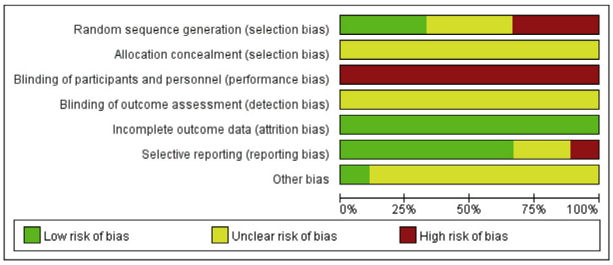

Figure 2 Risk of bias graph.

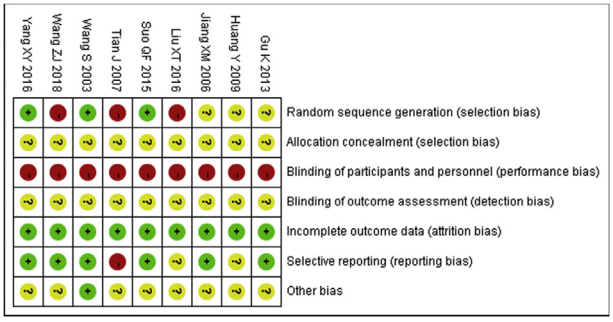

Figure 3 Risk of bias summary.

UPDRS III

Five trials[19,20,22,25,26] reported motor function scores of patients using the UPDRS III (Table 2 and Supplementary Fig. 4). All these five trials used Madopar as the intervention measures. The meta-analysis of these studies showed that a combination of SEA and Madopar was more effective than Madopar alone for motor function improvement (MD: 5.75, 95% CI: 4.18 to 7.32, $P < .001$). No obvious heterogeneity existed ($P = .61$; $I^2 = 0\%$).

Adverse events

Only one RCT[25] described adverse events. In the experimental group, 31 out of 37 subjects had adverse reactions before treatment, compared with 13 out of 37 after treatment; in the control group, 31 out of 39 subjects had adverse reactions before treatment, while 32 out of 39 had adverse reactions after treatment. There were significant differences between the two groups ($P < .01$), indicating that SEA could relieve the side effects caused by medication.

Funnel plot analysis

The number of included trials was so small that we couldn't conduct a funnel plot analysis recommended by the guidelines in the *Cochrane Handbook of Systematic Reviews*.[17]

Discussion

Summary of the main results

Nine studies that assessed the effects of SEA therapy for PD treatment were included in this systematic review, incorporating 474 patients. In this systematic review, our meta-analysis of the effectiveness rate of six studies demonstrated that SEA combined with medication improved overall symptoms in PD patients. In addition, the overall therapeutic effects of SEA were evaluated by analyses using total UPDRS and Webster scale scores, and these analyses confirmed the previous finding. The MD of the total UPDRS

Table 2 Meta-analysis of the effects of SEA combined with medication vs medication alone.

Outcome or subgroup	Studies	Statistical method	Effect estimate (95%CI)	Test for overall effect	Heterogeneity
Total UPDRS	3	Mean Difference (IV, Random, 95% CI)	7.15 [0.24, 14.07]	$Z = 2.03$ ($P = .04$)	$I^2 = 52\%$
SEA + Madopar vs Madopar	2	Mean Difference (IV, Random, 95% CI)	11.01 [4.10, 17.91]	$Z = 3.12$ ($P = .002$)	$I^2 = 0\%$
SEA + L-Dopa vs L-Dopa	1	Mean Difference (IV, Random, 95% CI)	2.10 [-3.56, 7.76]	$Z = 0.73$ ($P = .47$)	N/A
Webster	2	Mean Difference (IV, Fixed, 95% CI)	1.60 [0.20, 2.99]	$Z = 2.24$ ($P = .03$)	$I^2 = 44\%$
SEA + Madopar vs Madopar	1	Mean Difference (IV, Fixed, 95% CI)	0.60 [-1.43, 2.63]	$Z = 0.58$ ($P = .56$)	N/A
SEA + L-Dopa vs L-Dopa	1	Mean Difference (IV, Fixed, 95% CI)	2.50 [0.57, 4.43]	$Z = 2.54$ ($P = .01$)	N/A
ER	6	Risk Ratio (M–H, Fixed, 95% CI)	1.35 [1.19, 1.54]	$Z = 4.50$ ($P < .001$)	$I^2 = 0\%$
SEA + Madopar vs Madopar	5	Risk Ratio (M–H, Fixed, 95% CI)	1.37 [1.19, 1.58]	$Z = 4.37$ ($P < .001$)	$I^2 = 0\%$
SEA + L-Dopa vs L-Dopa	1	Risk Ratio (M–H, Fixed, 95% CI)	1.21 [0.86, 1.71]	$Z = 1.12$ ($P = .26$)	N/A
UPDRS III	5	Mean Difference (IV, Fixed, 95% CI)	5.75 [4.18, 7.32]	$Z = 7.19$ ($P < .001$)	$I^2 = 0\%$
SEA + Madopar vs Madopar	5	Mean Difference (IV, Fixed, 95% CI)	5.75 [4.18, 7.32]	$Z = 7.19$ ($P < .001$)	$I^2 = 0\%$

Abbreviations: CI: confidence interval; ER: effectiveness rate; IV: inverse variance; L-Dopa; L-3,4-dihydroxypheylalanine; M-H: Mantel-Haenszel; N/A: not applicable; RR: risk ratio; SEA: scalp electro-acupuncture; UPDRS: Unified Parkinson Disease Rating Scale.

was much higher than the minimal clinically important difference (MCID), which is the smallest clinically meaningful change for patients in a specified outcome measure.[29,30] In terms of motor dysfunction, five studies[19,20,22,25,26] reported positive results using the UPDRS III, and the outcome suggested that SEA combined with medication had a significant improvement on motor symptoms compared with medication alone. In addition, the MD from UPDRS III scores was 5.75, which is within the moderate range of a clinically important difference (4.5—6.7), thus demonstrating a clinically meaningful change in motor function in response to therapeutic interventions.[29] No adverse events related to SEA were reported; in contrast, one study showed that SEA had the effect of relieving side effects caused by medications. Currently, our results suggest that EA stimulation at scalp acupoints combined with medication is a relatively safe therapy that can alleviate motor and overall symptoms when compared with treatment with medication alone. However, due to the poor methodological quality of studies and the small number of included trials, no definite conclusions can be made. A number of high-quality RCTs that focus on SEA therapy for PD management are thus needed in future.

Strengths and limitations of this review

To include the most comprehensive set of experiments possible, we searched a series of electronic databases without language restrictions in a systematic evaluation. To our knowledge, this meta-analysis is the first to evaluate the effects and safety of SEA combined with medication in the treatment of PD.

However, we were unable to reach a definitive conclusion regarding the effectiveness of SEA because of a number of limitations in this systematic review and meta-analysis. First, the selected studies were all carried out and published in China, and no unpublished trials or articles using patients of different races were found. This may affect the application of the results to an international population. Second, the methodological quality of the included trials was low, which probably led to an overestimation of the therapeutic effect of combination SEA and medication therapy in the treatment of PD. Third, no articles described the methods of sample size calculation, which increases uncertainty regarding the overall evidence for SEA treatment of PD. Fourth, the treatment conditions in the included trials were different. For example, the disease duration ranged from 2.4 to 8 years, and was not reported in one study; for the medications, only one article used L-Dopa as the control therapy, while the other studies all used Madopar; for treatment duration, the majority of studies had a treatment duration of 4 weeks, while the remaining studies varied from 5 to 12 weeks; and for the acupoints used, these varied between studies, and included MS6, GB 20, MS8, MS9, MS4, and MS14, among others. Fifth, the reporting outcomes varied between studies. Different outcome parameters were employed, such as the total UPDRS and Webster scale scores. Furthermore, only one RCT[25] reported adverse reactions, and this study gave no specific description of the types and characteristics of reactions, and only provided the case numbers of adverse reactions. In addition, none of the included RCTs provided follow-up data. To determine whether SEA is truly effective in treating PD, any future evaluation of its therapeutic effectiveness should be in accordance with international standards.

Implications for future studies

With recent advances in pharmacological therapies and surgery for the treatment of PD, there is growing concern over the consequent adverse events. Long-term L-Dopa therapy causes side effects in both motor and non-motor responses, the former including ON—OFF fluctuations, sudden and unpredictable changes in mobility, and the wearing-off phenomenon.[31] Furthermore, deep brain stimulation can cause a number of complications, such as intracerebral hemorrhage, which can induce serious neurologic symptoms.[32] Thus, with increasing interest worldwide in alternative medical therapies to treat PD, attention has been drawn to the effects of SEA, which is a complementary and alternative medical therapy that is supported by scientific evidence, and which is growing to be accepted by modern medicine.[33]

At present, one of the most commonly used method of acupuncture and moxibustion treatment in PD is scalp acupuncture, which accounts for 58.3% of the frequency of the main points.[34] In this review, we found that MS6, GB 20, MS8, MS9, MS4, and MS14 were the most frequently used acupoints. Both MS6 and GB 20 were used in four studies each. The main clinical symptoms of PD are associated with motor dysfunction, such as tremor or rigidity. The MS6 line (the posterior oblique parietal—temporal line) relates to the primary motor area, which is responsible for motor symptoms in PD. This line goes from *Qianshencong* (EX-HN1) to *Xuanli* (GB 6) and can be divided as follows: (i) the upper 1/5, corresponding to the inferior limbs and torso; (ii) the middle 2/5, corresponding to the superior limbs; and (iii) the lower 2/5, corresponding to the face and language.[10] The MS14 line (the lower lateral line of the occipital scalp), which is a line of 2 *cun*, goes down from *Yuzhen* (BL 16), corresponding to the balance area, and can be used to treat equilibrium disturbances, which are a common clinical motor dysfunction in PD.[35] Recent evidence suggests that PD patients also have changes in sensory[36] and autonomic function.[37] The former consists of tactile abnormalities, pain, thermal abnormalities, proprioceptive abnormalities,[38] and evokes potential abnormalities, and the latter includes cardiovascular, urogenital, gastrointestinal, and thermoregulatory disorders.[39] GB 20 is a common point for the treatment of sensory deficits and autonomic dysfunctions in PD, including occipital pain and stiffness, headaches, vertigo, and dizziness.[40] GB 20 is an intersecting point of gallbladder meridian and *Yangwei* meridian, and is located at the height of the bottom line of the occipital protuberance, 2.25 *cun* lateral to the midline (the line of the pupil), and in the depression between the sternocleidomastoid and trapezius muscles.[41] For disturbed autonomic function in PD, the MS4 line (lateral line III on the forehead) can be used to treat sexual dysfunction, urinary frequency, and constipation, because it goes down

from the point 0.75 *cun* lateral to *Touwei* (ST 8), which corresponds to the reproductive and intestinal regions.[42] There are also acupoints that are related to both motor and non-motor dysfunction. The MS8 line (lateral line I of the vertex) goes backward from *Tongtian* (BL 7) to a distance of 1.5 *cun*, corresponds to the region of lumbar area, legs, and feet, and can be used to treat paralysis, numbness, and pain. The MS9 line (lateral line II of the vertex) goes backward from *Zhengying* (GB 17) to *Chengling* (GB 18) with a distance of 1.5 *cun*, corresponds to the region of the shoulders, arms, and hands, and can be used to treat headaches, migraine paralysis, numbness, and pain.

Based on our analysis, SEA combined with medications exerted neuroprotective effects. For instance, the effectiveness rate, and total UPDRS and Webster scale scores were significantly improved when medication was combined with SEA treatment compared with medication alone. The potential mechanism by which SEA and medication as an adjuvant treatment increased therapeutic effects may be related to the possible complementary effect of the two interventions in the regulation of dopaminergic and non-dopaminergic pathways. It is also possible that SEA lifts the restrictions on abnormal synaptic plasticity,[43] D3 striatum dopamine receptors decrease, and progressive loss of dopaminergic neurons that occur with L-Dopa treatment. Other possible mechanisms of SEA are as follows: (i) it improves blood flow in the frontal lobe, cervical lobe, and occipital lobe, thus promoting neuronal metabolism[44]; (ii) it protects dopaminergic neurons by increasing the dopamine transporter content in the basal ganglia[45]; (iii) it halts the degeneration of dopaminergic neurons in the substantia nigra and upregulates brain derived neurotrophic factor mRNA levels in the ventral midbrain, thus regenerating the injured dopaminergic neurons by activating endogenous neurotrophins[46]; (iv) it inhibits the activation of microglia and inflammation in PD[47]; (v) it enhances GABAergic inhibition in the output structure of the basal ganglia[48]; (vi) it protects the nigrostriatal system through anti-oxidative and anti-apoptotic effects[49,50]; (vii) it protects and regulates the motor circuits in the brain.[51]

Conclusion

SEA combined with medication can exert considerable effects in the treatment of PD, including improvements in the effectiveness rate and the total UPDRS and Webster scale scores. In addition, the adjuvant SEA treatment group had a greater improvement in motor function, represented by the UPDRS III score, than medication alone. These results are encouraging; however, because of the relatively low number and poor methodological quality of the primary trials, the results should be viewed with caution. Therefore, large in sample size, strictly designed RCTs using unified acupuncture points that follow the guidelines of CONSORT and STRICTA are urgently needed to prevent heterogeneity and produce high-quality evidence.

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Conflicts of interest

The authors do not have any competing interest.

CRediT authorship contribution statement

Tianyao Qiang: Writing – original draft, methodology, and formal analysis. **Cong Gai:** Data curation, funding acquisition, and Writing – review & editing. **Hongmei Sun:** Conceptualization, funding acquisition, and supervision. **Yuan Chai:** Data curation and formal analysis. **Wandi Feng:** Resources and data curation. **Haojie Ma:** Resources and data curation. **Yi Zhang:** Resources and formal analysis. **Jing Feng:** Software and formal analysis. **Zhenyu Guo:** Methodology. **Ling Ma:** Software.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtcms.2019.01.005.

References

1. Nussbaum RL, Ellis CE. Alzheimer's disease and Parkinson's disease. *N Engl J Med*. 2003;348(14):1356–1364.
2. Fernandez HH. 2015 Update on Parkinson disease. *Cleve Clin J Med*. 2015;82(9):563–568.
3. Ossig C, Reichmann H. Treatment strategies in early and advanced Parkinson disease. *Neurol Clin*. 2015;33(1):19–37.
4. Wei YJ, Stuart B, Zuckerman IH. Use of antiparkinson medications among elderly Medicare beneficiaries with Parkinson's disease. *Am J Geriatr Pharmacother*. 2010;8(4):384–394.
5. Hamani C, Florence G, Heinsen H, et al. Subthalamic nucleus deep brain stimulation: basic concepts and novel perspectives. *eNeuro*. 2017;4(5). pii:ENEURO.0140-17.2017.
6. Zhang AH, Sun H, Yan GL, Cheng WP, Wang XJ. Systems biology approach opens door to essence of acupuncture. *Complement Ther Med*. 2013;21(3):253–259.
7. Adams JD. The effects of yin, yang and qi in the skin on pain. *Medicines (Basel)*. 2016;3(1):E5.
8. Van Hal M, Green MS. *Acupuncture*. Treasure Island, FL: StatPearls Publishing; 2018.
9. Zeng BY, Salvage S, Jenner P. Current development of acupuncture research in Parkinson's disease. *Int Rev Neurobiol*. 2013;111:141–158.
10. Zanardi R, Maieron M, Tomasino B. Modulation of hand motor-related area during motor imagery and motor execution before and after middle 2/5 of the MS6 line scalp acupuncture stimulation: an fMRI study. *Brain Cogn*. 2016;103:1–11.
11. de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *Lancet Neurol*. 2006;5(6):525–535.
12. Liu XX, Zhang XZ, Nie K, et al. Effect of electro-scalp acupuncture on acute ischemic stroke: a randomized, single blind, trial. *J Tradit Chin Med*. 2018;38(1):95–100.
13. Zhang H, Zhao L, Yang S, et al. Clinical observation on effect of scalp electroacupuncture for mild cognitive impairment. *J Tradit Chin Med*. 2013;33(1):46–50.
14. Huang Y, Jiang X, Zhuo Y, Wik G. Complementary acupuncture in Parkinson's disease: a spect study. *Int J Neurosci*. 2010;120(2):150–154.

15. Fahn S, Elton RL. Unified Parkinson's disease rating scale. In: Fahn S, Mardsen CD, Jenner P, Teychenne P, eds. *Recent Developments in Parkinson's Disease*. New York, NY: Raven Press; 1986:375.
16. Webster DD. Critical analysis of the disability in Parkinson's disease. *Mod Treat*. 1968;5(2):257—282.
17. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions (Version 5.1.0; updated March 2011)*. The Cochrane Collaboration; 2011. Available from: http://handbook.cochrane.org. Accessed August 6, 2018.
18. *Review Manager (RevMan) [Computer Program] Version 5.3*. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration; 2014. Available from: http://ims.cochrane.org/revman/download. Accessed August 8, 2018.
19. Gu K, Liu K, Lu ZY, Fan XP, Zong L. Clinical observations on combined treatment of Parkinson's disease using acupuncture and medicine. *Shanghai J Acupunct Moxibust*. 2013;32(12):993—995 [Chinese].
20. Huang Y, Zhuo Y, Jiang XM, et al. Effect of scalp acupuncture on regional cerebral blood flow in Parkinson's disease patients. *Chin J Tradit Chin Med Pharm*. 2009;24(3):305—308 [Chinese].
21. Jiang XM, Huang Y, Zhuo Y, Gao YP. Therapeutic effect of scalp electroacupuncture on Parkinson disease. *J South Med Univ*. 2006;26(1):114—116 [Chinese].
22. Liu XT, Wu W. Clinical effect observation of scalp electroacupuncture combined with levodopa-benserazide tablets in the treatment of Parkinson's disease with motor dysfunction. *Chin J Integr Med Cardio Cerebrovasc Dis*. 2016;14(22):2600—2602 [Chinese].
23. Suo QF, Wang LY, Peng MH. Clinical observation on 70 patients with Parkinson's disease treated by electro-acupuncture at neck points plus scalp. *J Basic Chin Med*. 2015;21(7), 860-861,883 [Chinese].
24. Tian J, Liu B. Clinical effect observation of scalp electroacupuncture in the treatment of Parkinson's disease. *Guangming J Chin Med*. 2007;22(1):38—39 [Chinese].
25. Wang S, Cai YY, Shang YJ, Lu JR. Effects of head point-through-point electroacupuncture on SOD and LPO in the patient of Parkinson's disease. *Zhongguo Zhen Jiu*. 2006;26(4):240—242 [Chinese].
26. Wang ZJ, Zhang LY, Chen J, Xu BZ. Therapeutic effect of scalp electroacupuncture combined with benserazide on 30 cases of Parkinson's disease symptoms of myotonia. *China Health Stand Manag*. 2018;9(7):104—105 [Chinese].
27. Yang XY. Efficacy of electroacupuncture combined with levodopa in the treatment of Parkinson's disease. *Chin J Pract Nerv Dis*. 2016;19(13):103—105 [Chinese].
28. Du BJ, Xie ZM. Analysis on common problems in clinical evaluation of new Chinese medicines and countermeasures. *J Tradit Chin Med*. 2009;50(12):1075—1078 [Chinese].
29. Shulman LM, Gruber-Baldini AL, Anderson KE, Fishman PS, Reich SG, Weiner WJ. The clinically important difference on the unified Parkinson's disease rating scale. *Arch Neurol*. 2010;67(1):64—70.
30. Hauser RA, Gordon MF, Mizuno Y, et al. Minimal clinically important difference in Parkinson's disease as assessed in pivotal trials of pramipexole extended release. *Parkinsons Dis*. 2014:467131.
31. Bastide MF, Meissner WG, Picconi B, et al. Pathophysiology of L-dopa-induced motor and non-motor complications in Parkinson's disease. *Prog Neurobiol*. 2015;132:96—168.
32. Park CK, Jung NY, Kim MS, Chang JW. Analysis of delayed intracerebral hemorrhage associated with deep brain stimulation surgery. *World Neurosurg*. 2017;104:537—544.
33. Wang Y, Xie CL, Wang WW, et al. Epidemiology of complementary and alternative medicine use in patients with Parkinson's disease. *J Clin Neurosci*. 2013;20(8):1062—1067.
34. Ren HY, Wang XX, Zheng Y, Huang Y. Exploration of regularities in point selection for acupuncture treatment of Parkinson disease. *Shanghai J Acupunct Moxibust*. 2015;34(1):70—72 [Chinese].
35. Sveinbjornsdottir S. The clinical symptoms of Parkinson's disease. *J Neurochem*. 2016;139(suppl 1):318—324.
36. Conte A, Khan N, Defazio G, Rothwell JC, Berardelli A. Pathophysiology of somatosensory abnormalities in Parkinson disease. *Nat Rev Neurol*. 2013;9(12):687—697.
37. Jost WH. Autonomic dysfunction in Parkinson's disease: cardiovascular symptoms, thermoregulation, and urogenital symptoms. *Int Rev Neurobiol*. 2017;134:771—785.
38. Cury RG, Galhardoni R, Fonoff ET, et al. Sensory abnormalities and pain in Parkinson disease and its modulation by treatment of motor symptoms. *Eur J Pain*. 2016;20(2):151—165.
39. Pfeiffer RF. Management of autonomic dysfunction in Parkinson's disease. *Semin Neurol*. 2017;37(2):176—185.
40. Aroxa FH, Gondim IT, Santos EL, Coriolano MD, Asano AG, Asano NM. Acupuncture as adjuvant therapy for sleep disorders in Parkinson's disease. *J Acupunct Meridian Stud*. 2017;10(1):33—38.
41. Chen S. Clinical application of fengchi point. *J Tradit Chin Med*. 2003;23(2):140.
42. World Federation of Acupuncture-Moxibustion Societies. Scalp acupuncture manipulations (WFAS STANDARD-004: 2012). *World J Acupunct Moxibust*. 2013;23(3):32—38.
43. Lei H, Toosizadeh N, Schwenk M, et al. A pilot clinical trial to objectively assess the efficacy of electroacupuncture on gait in patients with Parkinson's disease using body worn sensors. *PLoS One*. 2016;11(5), e0155613.
44. Wang S, Zhou ZK, Hu BC, et al. Clinical study of head point-through-point electroacupuncture for treatment of Parkinson's disease. *Zhongguo Zhen Jiu*. 2003;23(3):129—131 [Chinese].
45. Huang Y, Jiang XM, Li DJ. Effects on electro-scalp acupuncture on cerebral dopamine transporter in patients with Parkinson's disease. *Zhongguo Zhong Xi Yi Jie He Za Zhi*. 2006;26(4):303—307 [Chinese].
46. Liang XB, Liu XY, Li FQ, et al. Long-term high-frequency electro-acupuncture stimulation prevents neuronal degeneration and up-regulates BDNF mRNA in the substantia nigra and ventral tegmental area following medial forebrain bundle axotomy. *Brain Res Mol Brain Res*. 2002;108(1—2):51—59.
47. Kang JM, Park HJ, Choi YG, et al. Acupuncture inhibits microglial activation and inflammatory events in the MPTP-induced mouse model. *Brain Res*. 2007;1131(1):211—219.
48. Jia J, Li B, Sun ZL, Yu F, Wang X, Wang XM. Electro-acupuncture stimulation acts on the basal ganglia output pathway to ameliorate motor impairment in Parkinsonian model rats. *Behav Neurosci*. 2010;124(2):305—310.
49. Lv E, Deng J, Yu Y, et al. Nrf2-ARE signals mediated the antioxidative action of electroacupuncture in an MPTP mouse model of Parkinson's disease. *Free Radic Res*. 2015;49(11):1296—1307.
50. Wang H, Pan Y, Xue B, et al. The antioxidative effect of electro-acupuncture in a mouse model of Parkinson's disease. *PLoS One*. 2011;6(5), e19790.
51. Wang H, Liang X, Wang X, Luo D, Jia J, Wang X. Electroacupuncture stimulation improves spontaneous locomotor hyperactivity in MPTP intoxicated mice. *PLoS One*. 2013;8(5), e64403.